Seeing beyond 2020: an economic evaluation of contemporary and emerging strategies for elimination of *Trypanosoma brucei gambiense*

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Summary

Background ***Trypanosoma brucei (T b) gambiense*** **is targeted to reach elimination as a public health problem by 2020 and full elimination by 2030. To achieve these goals, stakeholders need to consider strategies to accelerate elimination. Hence, we aimed to model several options related to current and emerging methods for case detection, treatment, and vector control across settings to assess cost-effectiveness and the probability of elimination.**

Methods **Five intervention strategies were modelled over 30 years for low, moderate, and high transmission settings. Model parameters related to costs, efficacy, and transmission were based on available evidence and parameter estimation. Outcomes included disability-adjusted life-years (DALYs), costs, and long-term prevalence. Sensitivity analyses were done to calculate the uncertainty of the results.**

Findings **To reach elimination targets for 2020 across all settings, approaches combining case detection, treatment, and vector control would be most effective. Elimination in high and moderate transmission areas was probable and cost-effective when strategies included vector control and novel methods, with incremental cost-effectiveness ratios (ICERs) ranging from US$400 to $1500 per DALY averted. In low transmission areas, approaches including the newest interventions alone or in combination with tiny targets (vector control) were cost-effective, with ICERs of $200 or $1800 per DALY averted, respectively, but only strategies including vector control were likely to lead to elimination. Results of sensitivity analyses showed that allowing for biennial surveillance, reducing vector control maintenance costs, or variations of active surveillance coverage could also be cost-effective options for elimination, depending on the setting.**

Interpretation **Although various strategies might lead to elimination of *T b gambiense*, cost-effective approaches will include adoption of emerging technologies and, in some settings, increased surveillance or implementation of vector control.**

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Introduction

Human African trypanosomiasis, or sleeping sickness, is caused by *Trypanosoma brucei (T b) gambiense* and *T b rhodesiense*. Approximately 70 million people live in at-risk areas in sub-Saharan Africa.[1] According to Global Burden of Disease (GBD) data from the Institute for Health Metrics and Evaluation (IHME), human African trypanosomiasis contributes an estimated 560 262 disability-adjusted life-years (DALYs) to the global burden of disease and ranks sixth in reference to the number of deaths among neglected tropical diseases.[2] *T b gambiense* is primarily maintained in a human–tsetse cycle, whereas *T b rhodesiense* transmission entails a large spectrum of reservoir animals, mainly game. Thus, elimination efforts have primarily targeted *T b gambiense*.

In 2011, WHO published a roadmap towards overcoming the impact of ten neglected tropical diseases (NTDs),[3] and this commitment was renewed in January, 2012, as the London Declaration on Neglected Tropical Diseases, supported by the collaboration Uniting to Combat NTDs, became a new benchmark for elimination goals. It was then that the goal of control, described as reduction of disease to acceptable levels, was shifted to elimination, which pursues zero incidence in a defined geographical area.[4] Human African trypanosomiasis caused by *T b gambiense* was one of the diseases targeted for elimination as a public health problem by 2020, which is defined as less than one case per 10 000 people per year,[3,5] and complete elimination by 2030. As the year 2020 approaches, stakeholders committed to *T b gambiense* elimination have recognised that current interventions are resource-intensive, costly, and infeasible in remote or sociopolitically unstable areas, hindering foreseen elimination goals.[5–7] Moreover, with several emerging novel technologies and approaches for surveillance, diagnosis, treatment, and prevention (vector control) of *T b gambiense*, now is the time to investigate whether new technologies can accelerate elimination and, if so, how to allocate current resources to the right combination of interventions.[8]

We aimed to analyse the cost-effectiveness of strategies for control and elimination of human African trypanosomiasis caused by *T b gambiense* and to forecast the effect of these approaches on disease transmission. The outcomes presented here aim to assist decision makers

For **IHME GBD data** see http://www.healthdata.org/gbd-data-tool

For more on **Uniting to Combat NTDs** see http://unitingtocombatntds.org

Research in context

Evidence before this study

Efforts to estimate the financial resources needed for elimination of neglected tropical diseases have been done by WHO and collaborations including Uniting to Combat NTDs and *The Lancet* Commission on Investing in Health. Furthermore, in 2015 and 2016, several researchers used modelling exercises to investigate the probability of elimination with available interventions in west and central Africa. However, a full economic assessment of multiple interventions for human African trypanosomiasis caused by *Trypanosoma brucei (T b) gambiense* has not been attempted. Building on our previous work, in which we identified and considered new technologies as potential strategies to achieve elimination, we used a modelling approach to assess the cost-effectiveness and the probability of elimination of five intervention strategies.

Added value of this study

Our analysis shows that potential additional gains can be made with emerging technologies, particularly short or single-dose oral treatments (fexinidazole and the oxaborole compound SCYX-7158), rapid diagnostic tests, and tiny targets. We also addressed trade-offs between costs, health effects, and elimination timelines that need to be considered by decision makers. Additionally, our results indicate that strategic planning for elimination campaigns should be tailored to suit the transmission situation of a given focus.

Implications of all the available evidence

The results presented in this report harmonise the contributions of current and emerging technologies that will be available to eliminate sleeping sickness and show good value for money, hence providing national sleeping sickness control programmes and global funders with evidence-based solutions for the elimination of human African trypanosomiasis caused by *T b gambiense*.

For more on **The Lancet Commission** see http://globalhealth2035.org

in determining which strategies are most likely to lead to elimination and will show good value for money.

Methods

Potential strategies for control and elimination

Various scenarios of current interventions and emerging methods have been proposed for control and elimination of human African trypanosomiasis caused by *T b gambiense*.[9] We developed a series of strategies using these scenarios over time to ascertain which combination of interventions would be most likely to sustain control or accelerate towards elimination. After preliminary modelling (appendix pp 29–38), we identified five strategies as relevant options for control or elimination of human African trypanosomiasis caused by *T b gambiense*, which are depicted in figure 1 and described in the appendix (p 1).

See Online for appendix

Strategy A, "control", is one of two strategies recommended by WHO[5] and aims to bring the number of annual cases to an acceptable level. It focuses on screening and treating patients and reflects the current approach practised by most national sleeping sickness control programmes across sub-Saharan Africa. In strategy A, patients self-report to local health centres (referred to as passive surveillance) and active case-finding is done by teams of health workers who seek out patients living in affected areas (active surveillance). Diagnosis is done in public during in-village screening campaigns and requires blood testing for serological confirmation of antigens in response to the parasite. Blood tests are confirmed using the card-agglutination trypanosomiasis test (CATT). Patients who have a positive CATT undergo parasitological confirmation of the disease. If confirmation is received they are referred for lumbar puncture to check the cerebrospinal fluid, to differentiate if the disease is in the early stages of development (stage 1 disease) or if the parasite has entered the CNS (stage 2 disease). In October, 2016, the approved treatment for human African trypanosomiasis on WHO's essential drug list for stage 1 disease was pentamidine, whereas nifurtimox-eflornithine combination therapy was the first-line, parenteral treatment for patients who have progressed to stage 2.

Strategy B, "control plus tiny targets", is the second strategy recommended by WHO and incorporates vector control to supplement the screen-confirm-stage-treat approach. Tiny targets are small insecticide-impregnated screens measuring 0·5×0·25 m that are more cost-effective and easier to deploy than are their larger predecessors (1×1 m² target; panel).[10,11]

The remaining three strategies incorporate innovative approaches in relation to surveillance, diagnosis, and treatment for control of *T b gambiense*, which are expected to arrive between 2016 and 2019. Strategy C, "new technologies 2016", maintains strategy A until 2016, after which time case-detection will be switched to more flexible teams on motorbikes and diagnosis of disease will be done using a first-generation rapid diagnostic test algorithm (panel). Confirmation and staging will be done using the loop-mediated isothermal amplification (LAMP) technique, and treatment for the second stage of disease will switch to ten oral doses of fexinidazole. This process is continued until 2019, when fexinidazole will be considered for treatment of both stage 1 and 2 disease and a second-generation rapid diagnostic test will be available (panel). Strategy D, "new technologies 2016 and 2019", mirrors strategy C until 2019, when a new oxaborole compound, SCYX-7158, will be available for treatment of both stages of disease with one oral dose (panel). Finally,

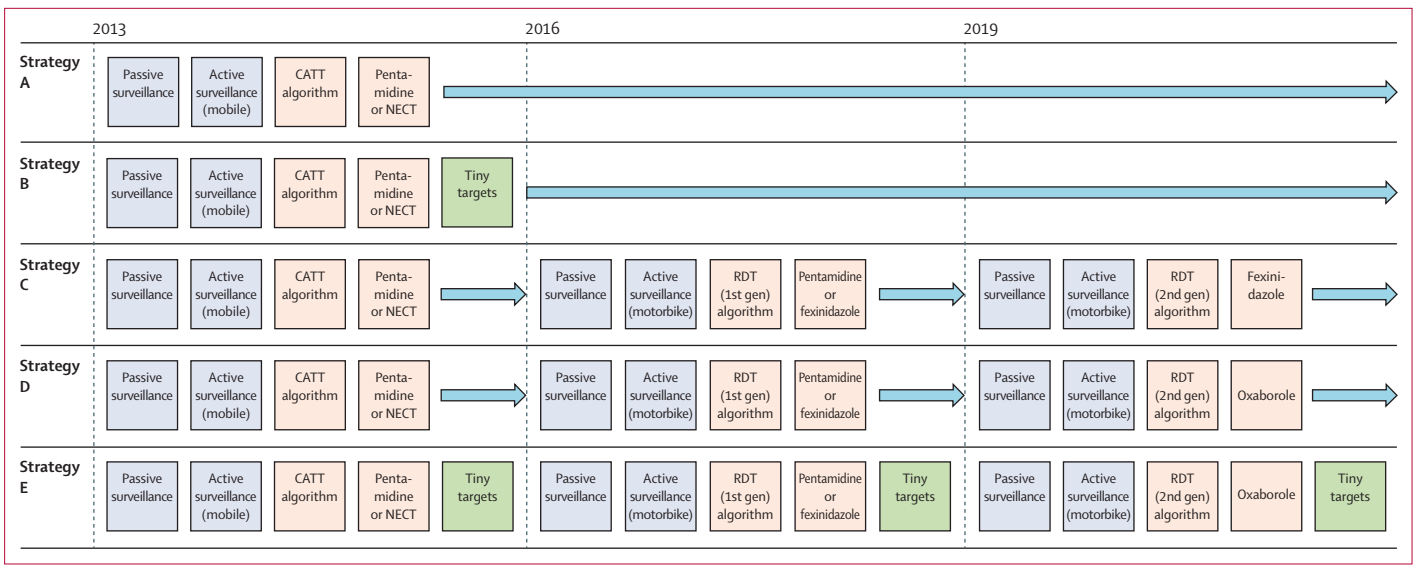

Figure 1: **Summary of potential strategies for control and elimination of human African trypanosomiasis caused by *T b gambiense***
Feasible scenarios are shown that could lead to elimination of human African trypanosomiasis caused by *Trypanosoma brucei (T b) gambiense*, based on current interventions and those in the pipeline.[9] Every scenario contains a component of surveillance, diagnostics, and treatment interventions to interrupt transmission of *T b gambiense* for a population at risk. Passive surveillance is combined with annual active surveillance in high-risk areas and with biennial surveillance in moderate-risk areas. In low-risk settings, active surveillance is not done and reliance is solely on passive surveillance. These approaches are based on recommendations for *T b gambiense* control outlined by WHO.[5] For all scenarios when the model reaches elimination, it switches to passive surveillance only (the model assumes no reinvasion of cases or flies after elimination is reached). CATT=card-agglutination trypanosomiasis test. NECT=nifurtimox-eflornithine combination therapy. RDT=rapid diagnostic test.

Panel: Highlights of new treatments and emerging technologies used in the current modelling for control and elimination of human African trypanosomiasis caused by *Trypanosoma brucei gambiense*

2013: tiny targets
Traditional targets for vector control in the field are quite large and costly with respect to maintenance and deployment. New targets (Vestergaard-Frandsen, Lausanne, Switzerland) are significantly smaller in size and cost less than their larger predecessors.[10,12] Tiny targets are made of a blue fabric that attracts flies, which are then killed by the insecticide-impregnated screens.[13]

2016: motorbike surveillance teams
Surveillance teams comprised of one or two people on a motorbike are feasible with newer diagnostic technologies that are easy to carry in a backpack and do not need cold-chain storage. Motorbikes also increase coverage because they can reach areas large trucks cannot access due to roads in poor condition.[9]

2016: fexinidazole
Fexinidazole is a well tolerated oral treatment to be given for 10 consecutive days.[14] It is currently in phase 3 trials[15] in patients with human African trypanosomiasis stage 2 and stage 1 disease.

2016: rapid diagnostic test algorithm, 1st generation
First-generation rapid diagnostic tests have been made available.[16,17] This algorithm considers the potential of such tests in combination with loop-mediated isothermal amplification (LAMP), for which staging is done using blood instead of cerebrospinal fluid obtained through lumbar puncture.[9]

2019: rapid diagnostic test algorithm, 2nd generation
A second-generation rapid diagnostic test with recombinant antigens that needs no additional blood sample or lumbar puncture for parasitological staging and confirmation.[9]

2019: SCYX-7158
SCYX-7158 is an oxaborole compound currently being tested in a phase 1 clinical trial.[18] It is a single-dose oral tablet that aims to cure both disease stages of human African trypanosomiasis.[9]

strategy E, "new technologies 2016 and 2019 plus tiny targets", assesses the effect of combining strategy D with tiny targets. In strategies C, D, and E, we assumed that, by 2019, oral treatment will be appropriate for either stage of disease and, hence, parasitological confirmation for staging will no longer be necessary.

Based on recommendations by WHO,[5] we assumed that active screening was done annually in settings with high transmission and biennially in areas with moderate transmission, and that no active screening component was included in low transmission settings, where detection relies solely on passive surveillance. We also assumed that only passive surveillance would be implemented after elimination, until 2042. We did not model scenarios in which reinvasion of cases (tsetse fly or human) happened after elimination. We based our estimated timelines on

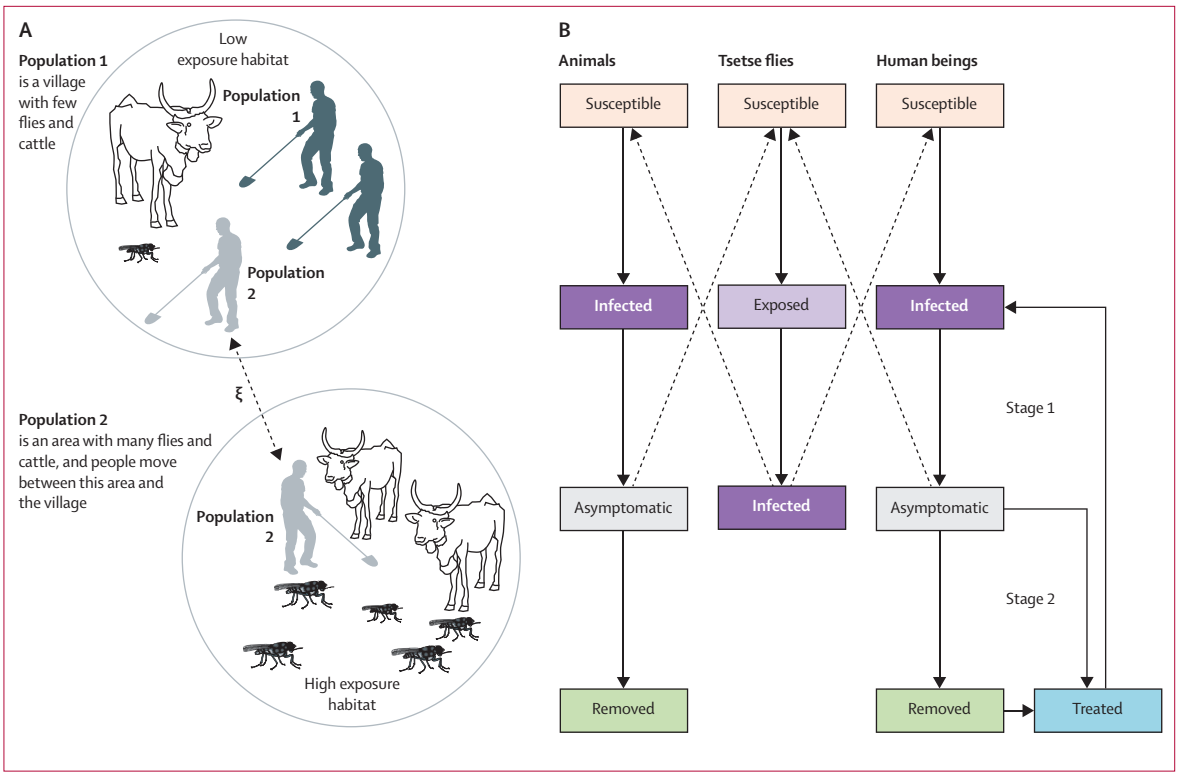

Figure 2: **Ordinary differential equation model**
(A) Heterogeneity captured by differing exposure levels of two populations living in the same area. Population 1 lives and works in a low-exposure habitat (eg, village). Population 2 commutes between habitats with low and high exposure, each harbouring tsetse and animal populations (eg, cattle) of varying sizes. (B) Transmission for populations in each habitat includes susceptible, infected, asymptomatic, and removed compartments (health states) for human beings, and susceptible, exposed, and infected compartments for tsetse flies (vectors).

every producer's estimate of products in the pipeline for human African trypanosomiasis caused by *T b gambiense* during 2013; hence, the timelines we present here are to be taken as examples because, in reality, technologies could arrive sooner or later on the market than planned. For example, a first-generation rapid diagnostic test arrived on the market in 2013 and has been used in endemic countries across sub-Saharan Africa since 2016. Moreover, evaluation of a second-generation rapid diagnostic test has been completed by the Foundation for Innovative New Diagnostics (FIND) and commercialisation is now expected in December, 2016, rather than 2019 as forecast.

For more on **FIND** see www.finddx.org

Health effect and economic modelling

To assess the long-term costs, health effects, and likelihood of the given strategies maintaining control or leading to elimination, we used an ordinary differential equation model of human African trypanosomiasis caused by *T b gambiense* (figure 2; appendix pp 11–13).[19] We divided the human population into several compartments: susceptible (ie, uninfected); infected (but not yet infective); asymptomatic (ie, stage 1 disease); removed (ie, stage 2 disease); or being treated. The asymptomatic state is not synonymous with the absence of symptoms in the clinical sense but is stated as such to differentiate the primary stage of the disease from the second, more severe, stage. We also tracked the number of people who died from human African trypanosomiasis over time and assumed that, although human beings have stage 2 disease or are being treated, they are generally recumbent and not present in tsetse habitat. We divided tsetse flies into susceptible, exposed, and infected compartments. We accounted for heterogeneity in exposure to tsetse bites by modelling two human populations, one in which individuals lived and worked in a low transmission setting and the other in which people travelled between a low transmission area and one with greater exposure to tsetse bites. A possible animal reservoir[1] was assumed to not contribute significantly to transmission of human African trypanosomiasis caused by *T b gambiense*. The model structure, transmission parameters for areas with high, moderate, and low transmission, and investigations of the use of current technologies to reach elimination have been described in detail elsewhere.[19] We fitted the model using a Bayesian importance resampling procedure to three stable prevalence levels that coincide with slightly above low (0·02%), moderate (0·112%), and high (1·61%) transmission areas, defined previously by WHO. Parameters that varied between the strategies related

to specific interventions are provided in the appendix (pp 3–5).[5]

For every model run, we allowed populations to reach a stable level of transmission over a 300-year period, in the absence of interventions. We then introduced interventions as specified by the different control and elimination strategies. If elimination was achieved in any run, we switched the interventions to post-elimination activities (passive surveillance). We tracked the disease burden attributable to human African trypanosomiasis by assigning a DALY value whenever an individual entered a relevant compartment (stage 1 disease, stage 2 disease, or death from disease). We calculated costs associated with interventions through incorporated cost functions.

Costing inputs, sources, perspective, and outcomes

Our analysis is from the perspective of a funder of a national sleeping sickness control programme; we modelled the annual prevalence, costs, and health outcomes (defined as DALYs)[20] over 30 years, starting in 2013 (appendix p 2). We discounted costs and DALYs at 3% annually[21,22] and assessed cost-effectiveness by calculating the incremental cost-effectiveness ratio (ICER) of each strategy relative to its next best comparator.

We developed a common unit for every intervention within a specific category then calculated a per diem cost based on cost functions for case detection, diagnostics, drug treatment, and vector control interventions. We took data inputs for direct costs from previous work,[23] country reports, expert opinions, and manufacturers, when estimates were not published or available publicly. Cost parameters and formulas for cost functions are available in the appendix (pp 3–5). We converted unit prices from countries other than the USA to US$ using purchasing power parity listed in the World Economic Outlook database,[24] and changed costs reported in € to US$ with the average exchange rate lists published on the European Central Bank Statistical Data Warehouse. We then inflated these values to 2013 prices with average consumer price indices.[24]

Uncertainty analysis

We did a probabilistic sensitivity analysis to establish the effect of parameter uncertainty on the cost-effectiveness and probability of elimination. We imputed parameters related to surveillance coverage, cost of interventions, cost of drug treatments, case-detection sensitivity, and cost and efficacy of vector control probabilistically based on latin hypercube sampling, and we ran 500 simulations. A full description of input parameters is provided in the appendix (pp 5–10).

We plotted probabilistic results as cost-effectiveness acceptability curves for low, moderate, and high transmission areas and reported the probability of elimination over the investigated period. We presented results in probabilistic terms and assessed them at two thresholds: elimination as a public health problem (less than one case in 10 000 people) by the year 2020; and full elimination (zero cases) by 2030. We did a one-way sensitivity analysis of discount rates, vector mortality, and coverage levels across all settings. Because we modelled no active surveillance in low transmission settings (based on WHO recommendations) in the base case analysis, we varied surveillance intensity in this setting to ascertain the potential effect on elimination and cost-effectiveness.

Previously, another molecule in development for human African trypanosomiasis failed to reach the market in late phase trials.[25,26] Therefore, we modified and modelled the strategies to assess the potential effect of the oxaborole compound SCYX-7158 experiencing market failure. Furthermore, clinical trials for fexinidazole are underway (NCT02169557); hence, we decided to investigate the potential effect on elimination if fexinidazole arrives on the market earlier than expected (to capture putative positive effects of ongoing trials).

	Total costs (US$) per person	Total DALYs per person	Incremental cost-effectiveness ratio
High transmission area			
Strategy D, new technologies 2016 and 2019	45·49 (44·82–46·15)	0·22 (0·22–0·23)	..
Strategy C, new technologies 2016	47·39 (46·28–48·50)	0·25 (0·23–0·26)	Dominated by strategy D
Strategy E, new technologies 2016 and 2019 plus tiny targets	61·29 (59·15–63·44)	0·18 (0·18–0·19)	$386 per DALY averted*
Strategy B, control plus tiny targets	82·34 (77·83–86·85)	0·20 (0·19–0·20)	Dominated by strategy E
Strategy A, control	114·87 (110·89–118·85)	0·34 (0·31–0·38)	Dominated by strategy E
Moderate transmission area			
Strategy D, new technologies 2016 and 2019	20·22 (19·94–20·50)	0·03 (0·03–0·03)	..
Strategy C, new technologies 2016	20·39 (20·10–20·68)	0·03 (0·03–0·03)	..
Strategy E, new technologies 2016 and 2019 plus tiny targets	37·60 (36·16–39·05)	0·02 (0·02–0·02)	$1509 per DALY averted*†
Strategy B, control plus tiny targets	48·01 (45·53–50·49)	0·02 (0·02–0·02)	Dominated by strategy E
Strategy A, control	55·18 (53·80–56·55)	0·04 (0·04–0·05)	Dominated by strategy E
Low transmission area			
Strategy C, new technologies 2016	2·26 (2·12–2·40)	0·04 (0·03–0·04)	..
Strategy A, control	2·52 (2·37–2·67)	0·04 (0·04–0·05)	Dominated by strategy C
Strategy D, new technologies 2016 and 2019	2·97 (2·78–3·15)	0·03 (0·03–0·03)	$160 per DALY averted†
Strategy E, new technologies 2016 and 2019 plus tiny targets	42·39 (39·75–45·04)	0·01 (0·01–0·01)	$1812 per DALY averted*
Strategy B, control plus tiny targets	44·97 (41·07–48·86)	0·01 (0·01–0·01)	Dominated by strategy E

Data are mean (95% CI). DALY=disability-adjusted life year. *Relative to strategy D. †Relative to strategy C.

Table: **Analysis of the different strategies, by risk transmission area**

For the **European Central Bank Statistical Data Warehouse** see http://sdw.ecb.europa.eu

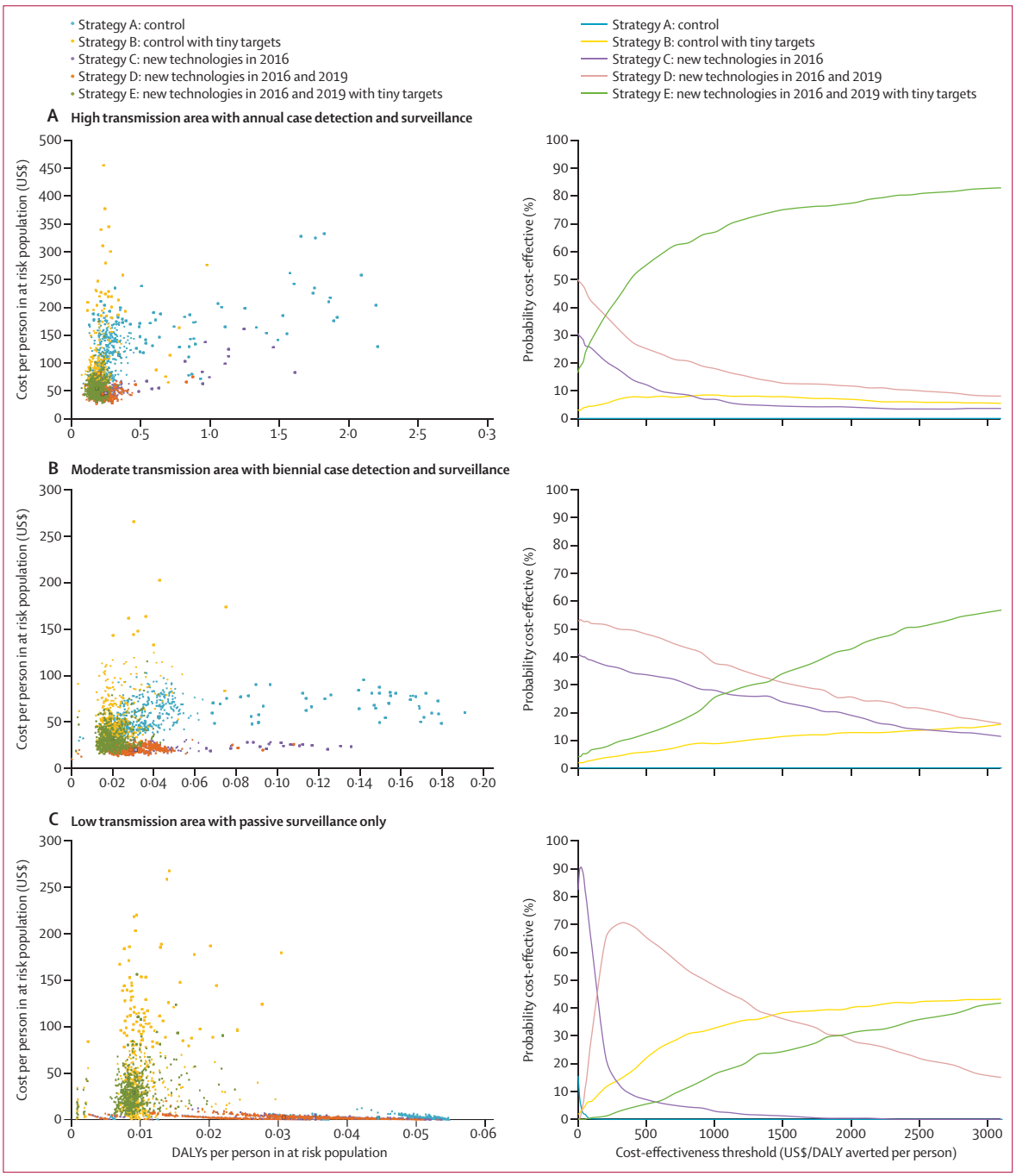

Figure 3: **Probabilistic sensitivity analysis**
Cost-and-effect planes (left) and cost-effectiveness acceptability curves (right) for areas of high, moderate, and low transmission. Dots in the cost-and-effect planes represents the outcome of costs per person versus disability-adjusted life years (DALYs) per person for every simulation. Mean results for every strategy are depicted as squares. The cost-effectiveness acceptability curves show the probability that a given strategy is cost-effective based on the net monetary benefit of every strategy at varying cost-effectiveness thresholds.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The table shows results from the base case analysis (appendix p 14). In high transmission settings, strategy E—comprising new technologies in 2016 and 2019 plus tiny targets—resulted in an ICER of $386 per DALY averted. In a moderate transmission setting, strategy E was also

cost-effective, at an ICER of $1509 per DALY averted. In low transmission areas, strategy D, consisting solely of new technologies in 2016 and 2019, resulted in an ICER of $160 per DALY averted; the next best approach after this one was strategy E, leading to an ICER of $1812 per DALY averted. Strategy A, the current control, was dominated consistently across settings, meaning that this approach costs more money and averted fewer DALYs.

Figure 3 shows variability surrounding mean costs and DALYs of every strategy and cost-effectiveness acceptability curves (appendix pp 20–25). In high transmission areas, at the cost-effectiveness threshold of $400 per DALY averted, strategy E had the highest probability of being cost-effective. In settings of moderate transmission, strategies D and E both had the highest probability of being cost-effective, at a threshold of $1500 per DALY averted. In low transmission settings, strategy D had the highest probability of being cost-effective, at a threshold of $200 per DALY averted, but at a threshold of $1800 per DALY averted, strategy B (in which tiny targets are added to current control efforts) had the highest probability of being cost-effective, competing with strategy E.

The results of the one-way sensitivity analysis are summarised in the appendix (pp 15–17). In high transmission areas, strategy E remained cost-effective over a range of parameter variations; however, the ICER for this approach decreased relative to base case estimates when mortality with tiny targets increased ($244 per DALY averted), when annual costs of vector control maintenance were reduced ($309 per DALY averted), when patients received oral treatments at home exclusively ($318 per DALY averted), or when active surveillance coverage was less than 80% ($49–205 per DALY averted). In areas of moderate transmission, strategy E also remained the most cost-effective option, with reductions in ICER from the base case analysis ranging from $317 to $1447 per DALY averted using the same parameter variations as for high transmission settings. In low transmission settings, strategy D typically remained the most cost-effective option across a range of parameter variations and was near to or lower than $100 per DALY averted either when maximum increases to passive surveillance were attributed to the arrival of fexinidazole on the market ($33 per DALY averted) or when biennial active surveillance campaigns were initiated ($123 per DALY averted).

Figure 4 shows that, in high transmission areas, achieving the London Declaration targets for elimination of *T b gambiense* by 2020 and full elimination in 2030 is probable (appendix pp 26–28). Particularly, strategies with vector control alone or vector control combined with new technologies (strategies B and E, respectively) have a more than 90% chance of reaching elimination in 2020 and 2030, whereas strategies including new technologies alone (strategies C and D) have an 80% chance. If regimens currently in place are maintained (strategy A), reaching elimination by 2020 or 2030 is less likely (roughly 50%). In areas of moderate transmission, all strategies have a more than 80% chance of reaching the London targets by 2020. Full elimination by 2030 would be feasible with strategies that include vector control (96%; strategies B and E), whereas adopting new interventions in the absence of tiny targets (68%; strategies C and D), or current control activities (roughly 50%; strategy A), are less likely to reach full elimination in the next few decades. Similar to moderate transmission settings, in areas of low transmission, achieving elimination as a public health problem is almost certain with strategies that include tiny targets (97–99%; strategies B and E). Adopting new technologies alone without vector control (strategies C and D) are unlikely to reach 2020 targets (24–45%) but are superior to the current control approach (0·05%; strategy A). Full elimination in low transmission areas will require strategies that include vector control (83–86%; strategies B and E), but will lead to delays in achieving elimination goals.

In high and moderate transmission areas, where active surveillance is maintained, a decrease in the effectiveness of vector control (from 5·49% to 1% mortality) would have no effect on elimination targets, however; in low transmission areas, ineffective vector control would render elimination elusive. Further improving the efficacy of targets (increase from 5·49% to 10%) would have relatively little effect compared with the base case analysis for high transmission areas but would guarantee elimination in moderate and low transmission settings with strategies that include vector control. Including active surveillance in addition to passive surveillance in low transmission areas, whether biennial or annual, would ensure that 2020 elimination targets will be achieved, but full elimination by 2030 is still most likely to occur with strategies that include vector control (appendix p 18). By contrast, the strategy currently in place (strategy A) is least likely to achieve full elimination. Varying the coverage of new technologies in low transmission zones had little effect relative to the base case results; however, an increase in treatment coverage with the oxaborole compound SCYX-7158 to approximately 45% led to a slight increase in the probability of elimination for strategies that included the oxaborole molecule (ie, strategies D and E) in these same areas. As provided in the appendix (pp 19, 20), coverage levels were varied in high and moderate transmission areas and showed overall that strategies with vector control (strategies B and E) would probably lead to elimination even when coverage was as low as 20%. Elimination as a public health problem (less than one in 10 000) was also achievable by 2030 when active screening coverage was equivalent to 60% and if oral tablet interventions become available (strategies C and D).

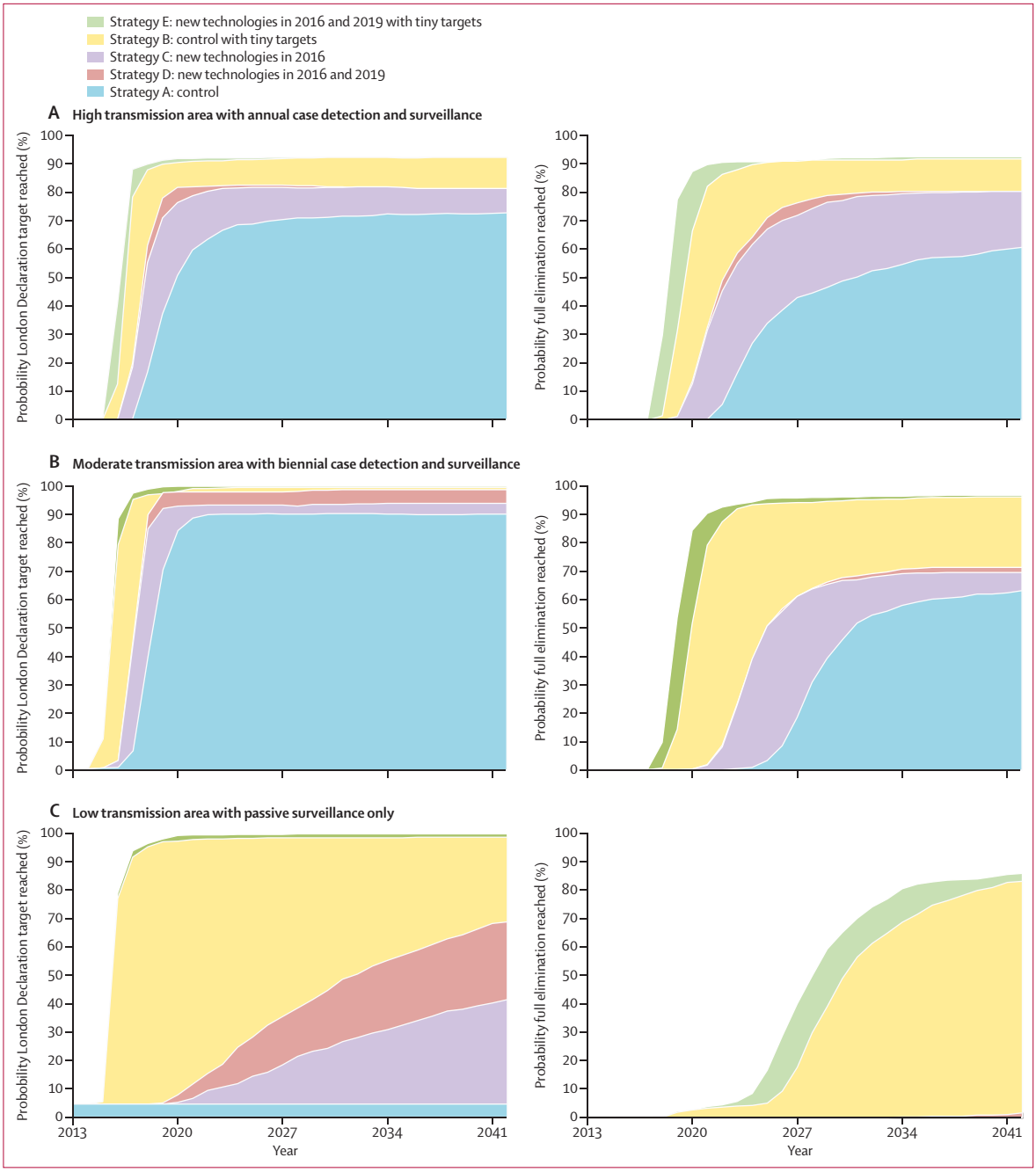

Figure 4: **Probability of reaching targets**
Probability of achieving London declaration targets (left) and full elimination (right) in areas of high, moderate, and low transmission. The London Declaration defines elimination, in concordance with the WHO roadmap, as either elimination as a public health problem or less than one case in 10 000 people.[3]

Discussion

Overall, our simulations show that continuing to screen and treat individuals for human African trypanosomiasis caused by *T b gambiense*, using currently available drugs and diagnostic methods (strategy A), is not cost-effective compared with alternative strategies that are becoming available. Although this approach might lead to control over the next four decades, it is less likely to reach full elimination across transmission settings by 2030. Adopting new interventions as they arrive on the market in combination with use of tiny targets (strategy E) is the most cost-effective approach for control and elimination of human African trypanosomiasis caused by *T b gambiense*, at a threshold appropriate for low-income and middle-income countries,[27] while leading to elimination goals in high transmission areas. In moderate

transmission zones, continually adopting new technologies as they arrive on the market alone (strategy D) or combined with tiny targets (strategy E) has a probability of being cost-effective near thresholds suitable for middle-income nations,[27] with both these strategies likely to achieve London Declaration targets; however, only strategy E is likely to reach full elimination. In low transmission areas, a conundrum for decision makers between cost-effectiveness and elimination persists. Adopting new interventions in the absence of vector control measures (strategy D) has the highest probability of being cost-effective at a threshold of $200 per DALY averted[21] but is unlikely to achieve short-term or long-term elimination targets. Adding tiny targets to current control measures (strategy B) or in combination with new technologies (strategy E) is more likely to lead to elimination but is only likely to be cost-effective at thresholds above $1500 per DALY averted.[27] These results highlight the economic constraints for global investments for elimination in areas with moderate and low transmission across sub-Saharan Africa. More than 98% of current cases of human African trypanosomiasis caused by *T b gambiense* are in low-income countries with a reported gross national income of roughly $400 per person annually,[27] whereas cost-effectiveness thresholds for global investors are closer to $300 per DALY averted.[21]

It is important to note that these insights are based on a limited number of strategies, for which results reflect the synergies of the input parameters available: in specific situations, current methods could well be adequate. For instance, elimination of human African trypanosomiasis caused by *T b gambiense* in Equatorial Guinea (Luba, Bioko Island) focused on a screen-and-treat campaign mechanism.[28] Furthermore, our results show that addition of active biennial surveillance in low transmission areas would be a cost-effective option, leading to elimination at less than $150 per DALY averted. Findings of field studies and modelling exercises[12,29–32] have confirmed our work, also showing that surveillance and treatment in combination with vector control can interrupt transmission in a shorter time span than can screen-and-treat campaigns alone. However, our analysis also examines the economic outcomes of these strategies, showing that although the cost-effectiveness of adding tiny targets will vary by setting, reducing vector control maintenance costs or varying surveillance coverage rates in combination with tiny targets could improve cost-effectiveness in high transmission areas while still possibly reaching elimination targets.

Many aspects of *T b gambiense* epidemiology remain elusive. For example, in recent years, the implications of asymptomatic carriers,[33,34] potential animal reservoirs for human African trypanosomiasis caused by *T b gambiense*,[33] case reports of congenital transmission,[35] systematic non-compliance of at-risk subgroups,[34,36] and the part played by vectors[34] have been considered or reconsidered. Changes to available evidence could potentially affect optimum elimination strategies, because our model assumes that animal reservoirs do not contribute significantly to transmission of *T b gambiense*,[19] that asymptomatic carriers are sufficiently rare in their occurrence,[37] that vectors do transmit *T b gambiense*, and that sexual transmission is infrequent. If additional evidence to the contrary becomes available, new modelling studies should be developed to assess the effect that these novel insights into the epidemiology of human African trypanosomiasis might have on elimination goals.

Our assessments of new technologies have been made in the hope that the foreseen molecules would reach the market. Fexinidazole is now in phase 3 trials,[15] with new studies for stage 2 human African trypanosomiasis in adults and children. Findings of interim analyses show that fexinidazole is on track to come to the market, with a high possibility that it might be available for both stages of the disease in 2019.[38] Furthermore, results from the one-way sensitivity analysis also showed that if oxaborole compounds fail to reach the market, fexinidazole in combination with new diagnostic methods would still be a cost-effective alternative likely to lead to elimination. Assuming that the oxaborole compound SCYX-7158 becomes available in the near future as a safe, single-dose oral compound, elimination becomes highly feasible and could possibly be considered as a tool for mass drug administration to prevent resurgence in areas that have high exposure rates to infected vectors. There is also uncertainty surrounding the sensitivity and specificity of current and emerging diagnostic tests, because diagnostic accuracy is related directly to prevalence and to identification by the diagnostic test of antibodies that the hosts produce. These difficulties within diagnostic methods have also hindered research and development of a rapid diagnostic test that can differentiate stages of disease, meaning that lumbar puncture might be necessary for a longer time than once hoped.

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Economic concerns still remain because emerging technologies might also need a change in the health-care structure of affected countries. Although our analysis assesses the cost-effectiveness of strategies, financing for a chosen strategy and assessing the budget effect that an elimination campaign would have on the current allotted fiscal space of decision makers are both necessary for global commitments towards elimination to be sustained.[39] The indirect costs to society also need to be assessed because new treatments and reduced transmission will decrease potential out-of-pocket expenditures for affected families[40] and reduce productivity losses for affected individuals. Moreover, reduction of tsetse flies could potentially afford communities access to land currently not inhabited, cultivated, or used for alternative economic gains.[41]

Progress reports for elimination show that cases of human African trypanosomiasis caused by *T b gambiense*

are on the decline,[42] which is a tribute to the concerted efforts of the global community working towards elimination of this disease. However, there are still populations living in at-risk areas not under surveillance. This situation calls for continued and swift diffusion of upcoming interventions in the pipeline across sub-Saharan Africa to further accelerate the decline of human African trypanosomiasis transmission and to ensure that 2020 targets and beyond become a reality.

Contributors

CSS, CMS, and FT designed the study. PS and MT contributed to development of the strategies modelled. CSS did the analysis and wrote the first draft of the report. All authors contributed to data interpretation and writing of the final report.

Declaration of interests

MT is chair of the board of the Drugs for Neglected Diseases initiative, which is leading development of fexinidazole and the oxaborole compound SCYX-7158 considered in our analysis. CSS, CMS, PS, and FT declare no competing interests.

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