Summary: Health economic evaluation of strategies to eliminate *gambiense* human African trypanosomiasis in the Mandoul disease focus of Chad

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Abstract

Human African trypanosomiasis, caused by the gambiense subspecies of Trypanosoma brucei (gHAT), is a deadly parasitic disease transmitted by tsetse. Partners from around the world have stepped up efforts to eliminate the disease, and the Chadian government have had a particular focus on the previously high-prevalence setting of Mandoul. In this study, we evaluate the economic efficiency of the intensified strategies that were put in place in 2014 aimed at interrupting transmission of gHAT, and we make recommendations on the best way forward based on both epidemiological projections and cost-effectiveness. In our analysis we use a dynamic transmission model fit to epidemiological data from Mandoul to evaluate the cost-effectiveness of combinations of active screening, improved passive screening (defined as an expansion of the number of health posts capable of screening for gHAT), and vector control activities (the deployment of Tiny Targets). For cost-effectiveness analyses, our primary outcome is disease burden, denominated in disability-adjusted life-years (DALYs), and costs, denominated in 2020 US$. Although active and passive screening have enabled more rapid diagnosis and accessible treatment in Mandoul, the addition of vector control provided good value-for-money (at less than $750/DALY averted) and substantially increased the probability of reaching the 2030 elimination target for gHAT as set by the World Health Organization. Our transmission modelling and economic evaluations suggests that gains have been made that could be maintained by robust passive screening, and the inclusion active screening and vector control strategies could be considered for other foci in the country with active transmission. Our analysis speaks to comparative efficiency, and it does not take into account all possible considerations; for instance, any cessation of on-going screening should first consider that screening will be critical to verify elimination of transmission and to protect against the possible importation of infection from neighbouring endemic foci.

E1 Introduction

After a decade of a steady but slow decline in case detection of gambiense human African trypanosomisis (gHAT) in the Mandoul region of Chad, the national gHAT control programme (Programme National de lutte contre la Trypanosomiase Humaine Africaine; PNLTHA-Chad) and international non-profit and academic partners introduced vector control (VC) in 2014 and improved passive screening (PS) in health facilities in 2015 [1–3].

In this study, we perform a retrospective cost-effectiveness analysis for the Mandoul focus of the intensified strategies starting in 2014 to understand the health economic implications if less ambitious strategies had been performed, as well as a sensitivity analysis to test if the decision would have been robust to earlier introduction of fexinidazole. Our subsequent prospective analysis then considers the health economic implications of what could be done against gHAT going forward from 2023 for Mandoul. We adopt a modelling framework in order to examine the interplay of epidemiological, economic and temporal factors in effective decision-making around gHAT strategies for elimination of transmission (EoT).

E2 Methods

E2.1 Strategies

The strategies for control are found in Table E1 for both the retrospective and prospective analysis. In the retrospective analysis, we considered the outcome of the strategy that was actually implemented, with improved PS and VC (*Imp. PS & VC*), to compare against less ambitious strategies. Alternative strategies included the interventions at levels present before 2014 (*Pre-2014*), as well as strategies that either only improved PS (*Imp.*

	Component Interventions					Scale-back criteria	
	ASd	ASe	PSd	PSe	VC	AS & VC	PS
Retrospective analysis							
Pre-2014	✓		✓			3y no P+	-
Imp. PS	✓		✓	✓		3y no P+	5y no P+
Addition of VC	✓		✓		✓	3y no P+	-
Imp. PS & VC	✓		✓	✓	✓	3y no P+	5y no P+
Prospective analysis							
Mean AS & VC (a)	✓		✓	✓	✓	3y no S+ or P+	5y no S+ or P+
Mean AS & VC (b)	✓		✓	✓	✓	3y no P+	5y no P+
Mean AS	✓		✓	✓		3y no P+	5y no P+
Max AS	✓	✓	✓	✓		3y no P+	5y no P+
Stop 2023 (No AS or VC)			✓	✓		-	5y no P+

Table E1: Strategies against gHAT in the Mandoul focus. Active screening (AS) coverage in the retrospective analysis is actual coverage in 2014–2019, and the recent mean coverage (2015–2019) thereafter – this is denoted as default coverage (ASd). Coverage in the prospective analysis is the recent mean (*Mean AS*) or the historical maximum for 2000–2019 (*Max AS*), which includes enhanced coverage (ASe). For passive screening (PS) PSd refers to default coverage, consistent with what was present before 2014 and PSe refers to enhanced coverage due to the clinics that were newly stocked with RDTs starting in 2015. Annually deployed vector control (VC) with around a 99% decrease in the population of tsetse in the first 4 months [4]. Treatment is given to all cases. Active screening algorithm specificity under *Mean AS & VC (a)* is 99.93% and for the strategies *Mean AS & VC (b)*, *Mean AS* and *Max AS* it is 100%. *Stop 2023 (No AS or VC)* signifies that AS and VC do not occur in 2023 onward. No P+/S+ indicates that both serological and confirmed cases must decline to 0 before scaleback. No P+ indicates that only cases confirmed by parasitology or trypanolysis must decline to 0 before scaleback.

PS) or only implemented VC (*Addition of VC*) alongside active screening (AS). In all strategies, the same amount of AS took place and the passive detection rate was at least the same as before 2014 or higher (*Imp. PS* and *Imp. PS & VC*).

In the prospective analysis, we look to alternative strategies that could be conducted going forward based on the actual situation in 2020 (analytical present, see Fig. E1) – therefore all these simulations include the intensified strategies that took place from 2014 combining AS, the expanded network of PS, and VC.

We simulated the impact of possible cessation of AS and VC starting in 2023 if no cases are observed for a given period of time, as indicated in Table E1. Under strategy *Mean AS & VC (a)*, AS and VC shut down when there are three years of neither S+ (serological positive) nor P+ (parasitology positive). For all other prospective strategies, AS and VC shut down after three years of no detected P+ cases, even if S+ cases continue to be diagnosed and treated with fexinidazole. We simulate reactive screening (RS) if subsequent parasitologically confirmed passive cases are detected in order to simulate the risk and size of the resurgence if vertical interventions are ceased mistakenly early. Finally we include a strategy that instantly stops both AS and VC regardless of case reporting (*Stop 2023 (No AS or VC)*).

E2.2 Model, health outcomes and costs

The original model fitting (2000–2019) and projections (2020–2040) [4] were modified to simulate costs and outcomes for Mandoul for the period of 2014-2040 for the retrospective analysis and for 2020–2040 for the prospective analysis. We used a variant of the "Warwick gHAT model", a previously published model that uses a mechanistic, deterministic modelling framework to explicitly simulate transmission between humans via tsetse.

Health burden is denominated in disability-adjusted life years (DALYs), a sum of years of life lost to disability (YLD) and of years of life lost among fatal cases (YLL). However, we also report cases and deaths.

Costs include fixed and variable costs of operation. Disease costs include diagnosis, confirmation, and staging via lumbar puncture, as well as the cost of the drug itself and the administration. We performed our analysis from the perspective of health- or intervention-delivery payers collectively.

E2.3 Economic evaluation and investment horizon

[A glossary of epidemiology and health economic terms is found in section E5]

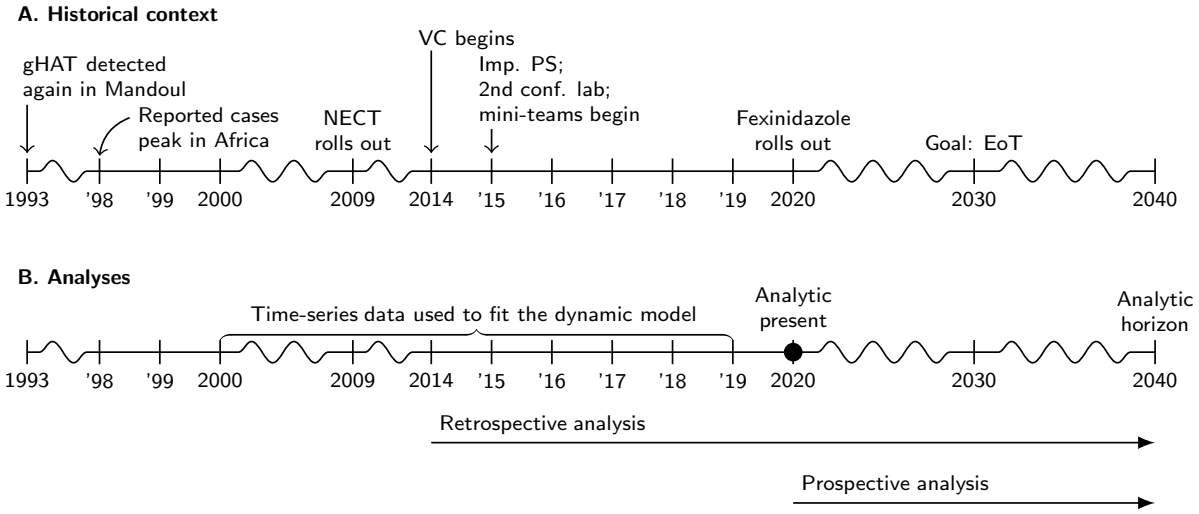

Figure E1: Timeline of gHAT epidemiology and analytic frame. A. Epidemiological information, start of new or improved interventions in Mandoul and the WHO 2030 goal. B. The years' of data were used to fit the model and the years corresponding to our retrospective and prospective analysis. NECT: Nifurtimox-eflornithine combination therapy, VC: vector control, Imp. PS: Improved passive screening, EoT: elimination of transmission.

We computed incremental cost-effectiveness ratios (ICERs) by taking the difference in costs and health effects (DALYs). As per recent recommendations from the WHO, we refrained from selecting a specific ICER that would be considered "cost-effective", and we aimed to make recommendations across a range of thresholds, known as willingness-to-pay thresholds, and after accounting for uncertainty.

We examined health and cost impacts in the long-term (2021–2040) to assess the returns on investments. Both costs and health outcomes are discounted at a yearly rate of 3%.

E3 Results

E3.1 Retrospective analysis

We ran a counterfactual scenario analysis to assess whether the increase in investment to gHAT activities in Mandoul from 2014 represented a good use of resources:

Health impact

- The model indicates that most deaths are from cases that were not detected, and consequently, not treated. It predicts that under the deployed intervention (*Imp. PS & VC*) 156 (95% PI: 72–255) occur between 2014-2040. The strategy implementing VC without improved PS (*Addition of VC*) would likely have already decreased undetected deaths to 181 (95% PI: 108–274) compared to the *Pre-2014* strategy which would have accumulated 2160 (95% PI: 1062–3689) undetected deaths. In contrast, *Improved PS* (without VC) would have only halved the number of undetected deaths to 943 (95% PI: 160–2444). An explanation of how undetected deaths are estimated and how they compare with detected deaths can be found in Figure E2 and in Supplementary Material S1 Text Section 1.2.3.
- DALYs are comprised primarily of deaths rather than years lived with disability. See Table E2.

Costs

- In 2015, it is estimated that costs increased by about 60% in order to institute the strategy conducted (*Improved PS & VC*) compared to the continuation strategy (*Pre-2014*). See Table E2.
- Over the 27-year period of 2014–2040, the total costs would have been expected to be highest had the *Improved PS* strategy been implemented (without VC) ($2.95M vs. $2.16M for the comparator).
- **Cost drivers**. If there had been a continuation of the *Pre-2014* strategy, costs would have been driven by AS, followed by the cost of treatment. If the *Improved PS* strategy had been adopted costs would

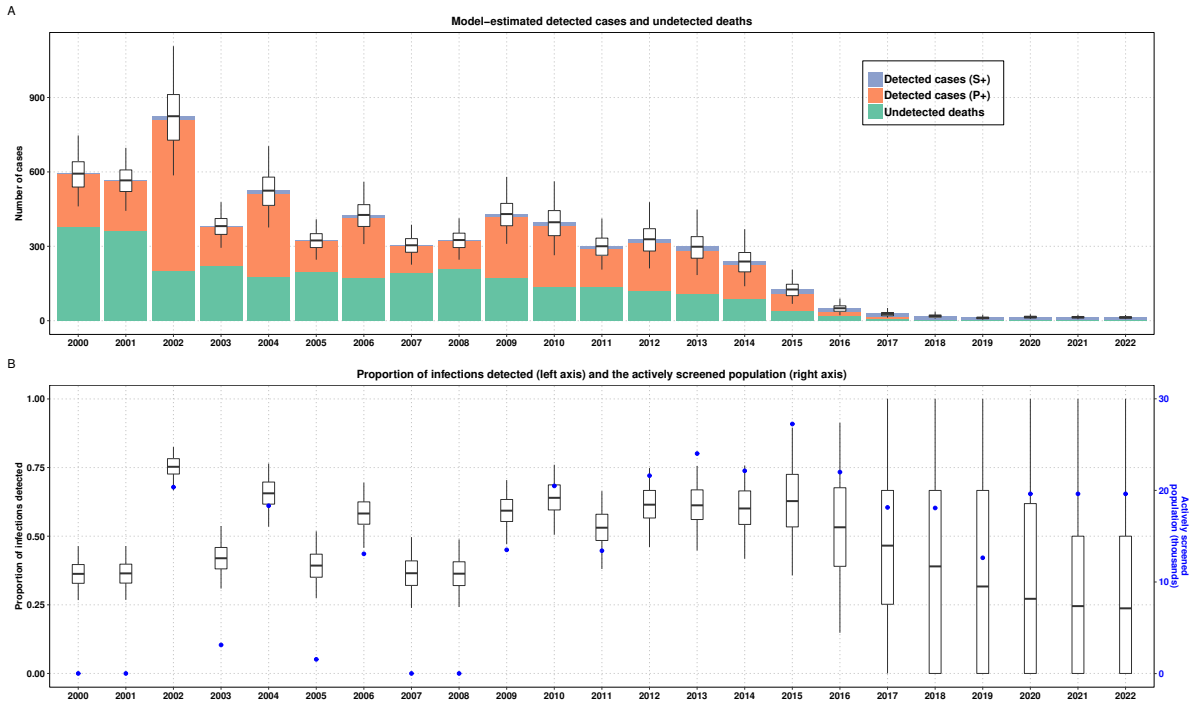

Figure E2: Comparison of detected cases and undetected deaths per year and their relationship to active screening intensity. A) detected cases (serological+), detected cases (parasitological+), and undetected deaths. Box and whisker plot shows the estimate, interquartile range, and 95% confidence interval of total numbers of cases reported and deaths. B) the proportion of infections (parasitological+ & deaths) detected and the population tested by moving units.

have been driven by both AS and PS. However, for strategies that include VC, costs were driven by VC but offset by substantial decreases in the cost of treatment, AS, and PS.

- We predict that the investment of VC without improved PS (the *Additional VC* strategy) would have yielded cost-savings by 2040, despite representing additional costs for the first few years (Figure E3).
- Estimates of the costs from 2014–2020 compared to the whole time horizon (2014–2040) can be seen in Figure E3C – the transparent colors indicate the amount that would be spent after 2021 compared to the solid colors, or the amount that would have already been spent 2014-2020.

Cost-effectiveness

- Compared to the *Addition of VC*, which is the minimum cost intervention, the *Improved PS & VC* strategy costs an additional $457,172 (after taking into account 3% yearly discounting), for an additional 612 DALYs averted; therefore the ICER for the Improved PS & VC strategy is $747 per DALY averted (see Figure E4). That is to say that while the investment in VC was cost-saving (*Addition of VC*), the investment in improved PS was cost-effective at a willingness-to-pay of $747 per DALY averted.
- Taking into account uncertainty, at $500 per DALY averted, there is a 31% probability that the implemented strategy was optimal, while at a WTP of $1000 per DALY averted, the probability that the strategy was optimal is 60%.

E3.2 Prospective analysis

We performed a prospective analysis to consider the health economic implications of what could be done against gHAT going forward from 2023 in Mandoul:

- Imperfect test specificity in AS (*Mean AS & VC(a)*) is very likely to incur direct costs in over-treatment, but those costs would be overshadowed by the inability to confidently cease vertical activities (*i.e* VC and AS) (See Figure E5).

	Pre-2014	Improved PS	Addition of VC	Improved PS & VC
Health effects				
Reported cases	2506 (1459, 3956)	1660 (787, 2959)	213 (119, 337)	238 (137, 363)
Deaths undetected	2160 (1062, 3689)	943 (160, 2444)	181 (108, 274)	156 (72, 255)
Cases total	4666 (2564, 7567)	2603 (989, 5341)	394 (253, 564)	394 (248, 569)
Deaths detected[a]	3 (1, 7)	2 (1, 5)	0 (0, 1)	0 (0, 1)
YLD	1709 (994, 2724)	797 (299, 1585)	126 (77, 190)	113 (62, 180)
YLL	97,383 (48,150, 166,497)	42,536 (7227, 110,235)	8162 (4844, 12,412)	7014 (3266, 11,570)
DALYs[b]	99,093 (49,395, 168,965)	43,334 (7716, 111,650)	8288 (4958, 12,559)	7127 (3370, 11,691)
Costs, in thousands US$				
AS costs	1167 (867, 1536)	1146 (823, 1523)	417 (300, 592)	416 (302, 580)
PS costs	67 (38, 107)	1162 (812, 1600)	67 (38, 107)	630 (451, 847)
VC costs	0 (0, 0)	0 (0, 0)	660 (296, 1206)	658 (291, 1199)
Treatment costs	930 (530, 1492)	642 (321, 1121)	121 (76, 181)	133 (85, 194)
Costs total	2164 (1630, 2832)	2949 (2209, 3722)	1265 (849, 1866)	1837 (1366, 2477)
EoT				
Year of EoT	After 2050	2043 (2029, After 2050)	2015 (2015, 2015)	2015 (2015, 2015)
Prob EoT 2030	<0.01	<0.01	>0.99	>0.99
Cost-effectiveness without uncertainty (discounted)[c]				
DALYs averted	0	20,739	35,682	36,294
Costs difference	0	570,807	-434,840	22,332
ICER	Dominated	Dominated	Min Cost	747
Cost-effectiveness with uncertainty, conditional on WTP[d]				
WTP: $0	0.06	0	0.94(p)	0
WTP: $250	0	0	0.95(p)	0.05
WTP: $500	0	0	0.69(p)	0.31
WTP: $750	0	0	0.50	0.50(p)
WTP: $1000	0	0	0.40	0.60(p)

[a] Detected deaths are those that occur due to treatment failure of loss-to-follow-up.
[b] DALYs are presented without discounting for reference.
[c] Cost-effectiveness results are given for discounted DALYs and costs as per convention.
[d] (p) is the preferred strategy; the strategy with the highest mean net monetary benefits

Table E2: Retrospective analysis. Summary of effects, costs, elimination of transmission (EoT) by 2030, and cost-effectiveness with and without uncertainty. Means are given along with 95% prediction intervals (PIs). YLL: years of life lost (to fatal disease), YLD: years of life lost to disability, DALYs: disability-adjusted life-years, PS: passive screening, AS: active screening, VC: vector control, ICER: incremental cost-effectiveness ratio, WTP: willingness to pay (USD per DALY averted), EoT: elimination of transmission.

- For all strategies with perfect diagnostic specificity, different combinations of interventions are predicted to make no difference in the number of cases detected (if there are any cases to be detected). See Table E3. Therefore, any strategies with interventions other than the basic continuation of PS are not computed to be cost-effective. What we conceive as the bare-minimum strategy, *i.e.* continuation of current PS until 5 years of no detections followed by the cessation of all vertical interventions in Mandoul, should cost around $398,000.
- If VC and AS continue until no more P+ cases are detected (*Mean AS & VC(b)*), the costs are predicted to be at most $676,000 for the period of 2021–2040.

E3.3 Scenario and uncertainty analysis

Interested readers can explore the results of scenario analysis related to horizons and discounting on the project website https://hatmepp.warwick.ac.uk/MandoulCEA/v2/. We performed a sensitivity analysis to see if the selection of the strategy with both improved PS and the addition of VC (*Imp. PS & VC*) would have been robust to an earlier introduction of cheaper and easier treatment in the form of fexinidazole. With fexinidazole treatment for eligible cases, the strategy *Addition of VC* would also be the minimum cost strategy and the strategy *Improved PS & VC* would also have an ICER of $747 per DALY averted (see Supplementary Information SI Text 3, Table B).

We also performed an analysis to examine the contribution of different factors to uncertainty. We found that the largest contributor to decision uncertainty and the most influential parameter (see Supplementary Information SI Text 3, Fig F) were the false positives considered stage 1 cases (S+ cases that would be P-), followed by undetected deaths and the number of false positives considered stage 2 cases (S+ cases that

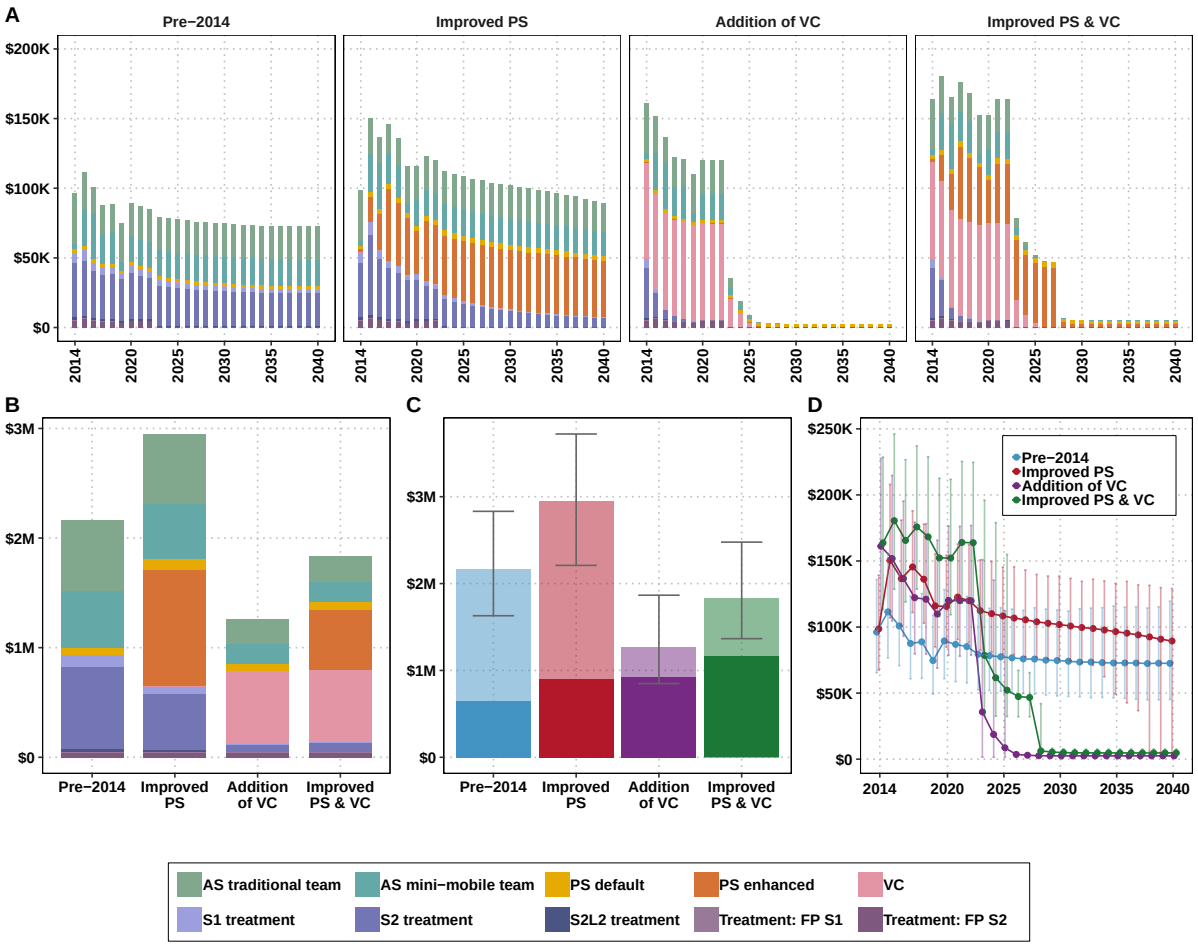

Figure E3: Costs by components of a strategy for the retrospective analysis: A) by year, B) for the period of 2014–2040, C) the costs for the period of 2014–2040 with uncertainty (transparent colors indicate the funds that have not been spent yet) and D) the total spent per strategy per year with 95% prediction intervals. See Supplementary Information S3 Text, Table A and Fig B for total estimates and uncertainty of the costs spent between 2014–2020 compared to the whole time horizon (2014–2040). AS: active screening, PS: passive screening, VC: vector control, FP: false positive, S1: stage 1, S2: stage 2, S2L2: stage 2 rescue treatment.

would be P-).

E4 Discussion

E4.1 Key findings

- Although new strategies for AS and PS have paved the way for better evaluation and more rapid and accessible treatment, interventions that included VC were good value-for-money and substantially increased the probability of reaching the EoT target. The VC that has already been deployed now should enable safe scale-back of AS, and therefore reduce the highest-cost component of the gHAT budget.
- Transmission modelling and economic evaluations suggest that it may be cost-effective to halt AS and VC as long as PS remains robust. The resources currently devoted to prevention and treatment of gHAT in Mandoul could be diverted to address the existing burden in Moissala and Maro.
- It is, however, critical to factor in the necessity of sufficient operations to carry out serological screening and parasitological confirmations to survey for possible importation of infection from neighbouring endemic foci.
- We also emphasise that we cannot know the costs of EoT verification as the procedures for verification

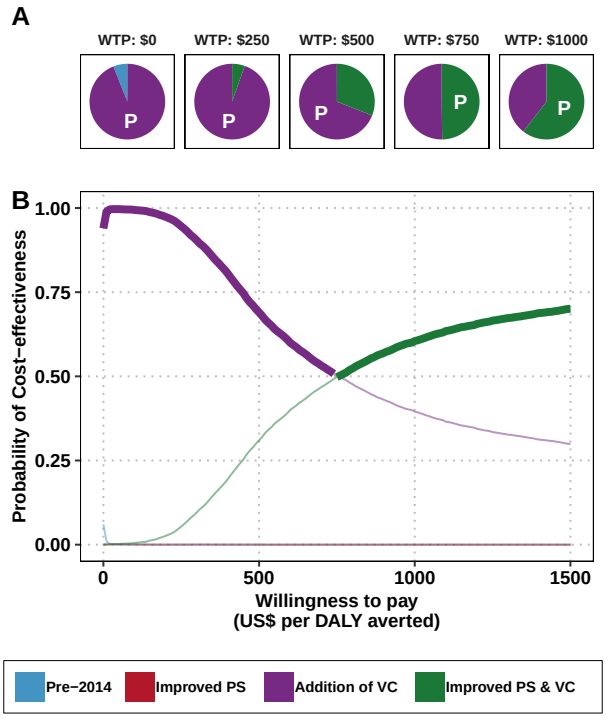

Figure E4: Uncertainty in cost-effectiveness for the retrospective analysis. A) Pie graphs depicting the probability that each strategy is optimal at the given willingness-to-pay (WTP) threshold. Strategies with the highest mean net monetary benefit are marked with a "P" for "preferred" strategy. B) Cost-effectiveness acceptability curves (CEACs) with the cost-effectiveness acceptability frontier (CEAFs) marked in bold. PS: passive screening, AS: active screening, VC: vector control, DALY: disability-adjusted life-years

are still to be confirmed.

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	Mean AS & VC (a)	Mean AS & VC (b)	Mean AS	Max AS	Stop 2023 (No AS or VC)
Health effects					
Reported cases	1 (0, 7)	1 (0, 7)	1 (0, 7)	1 (0, 6)	1 (0, 7)
Deaths undetected	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)
Cases total	1 (0, 8)	1 (0, 8)	1 (0, 8)	1 (0, 7)	1 (0, 8)
Deaths detected[a]	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
YLD	3 (2, 5)	1 (0, 1)	1 (0, 1)	1 (0, 1)	1 (0, 1)
YLL	26 (0, 133)	26 (0, 132)	26 (0, 134)	26 (0, 134)	26 (0, 134)
DALYs[b]	29 (2, 136)	26 (0, 133)	27 (0, 135)	27 (0, 134)	27 (0, 135)
Costs, in thousands US$					
AS costs	856 (641, 1122)	107 (66, 221)	107 (66, 221)	111 (66, 246)	0 (0, 0)
PS costs	933 (658, 1306)	391 (277, 539)	391 (277, 539)	391 (277, 540)	390 (278, 541)
VC costs	1379 (605, 2469)	170 (65, 401)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Treatment costs	73 (44, 109)	8 (4, 13)	8 (4, 13)	8 (4, 13)	8 (4, 13)
Costs total	3242 (2345, 4407)	676 (483, 1013)	505 (370, 694)	509 (370, 710)	398 (285, 548)
Cost-effectiveness without uncertainty (discounted)[c]					
DALYs averted	0	2	2	2	2
Costs averted	0	-1,863,141	-2,029,105	-2,025,592	-2,133,457
ICER	Dominated	3,838,240	Dominated	1,271,341	Min Cost
Cost-effectiveness with uncertainty, conditional on WTP[d]					
WTP: $0	0	0	0	0	0.99(p)
WTP: $250	0	0	0	0	0.99(p)
WTP: $500	0	0	0	0	0.99(p)
WTP: $750	0	0	0	0	0.99(p)
WTP: $1000	0	0	0	0	0.99(p)

[a] Detected deaths are those that occur due to treatment failure of loss-to-follow-up.
[b] DALYs are presented without discounting for reference.
[c] Cost-effectiveness results are given for discounted DALYs and costs as per convention
[d] (p) is the preferred strategy; the strategy with the highest mean net monetary benefits

Table E3: Prospective analysis. Summary of effects, costs, elimination of transmission (EoT) by 2030, and cost-effectiveness with and without uncertainty. Means are given along with 95% prediction intervals (PIs). YLL: years of life lost (to fatal disease), YLD: years of life lost to disability, DALYs: disability-adjusted life-years, PS: passive screening, AS: active screening, VC: vector control, ICER: incremental cost-effectiveness ratio, WTP: willingness to pay (USD per DALY averted)

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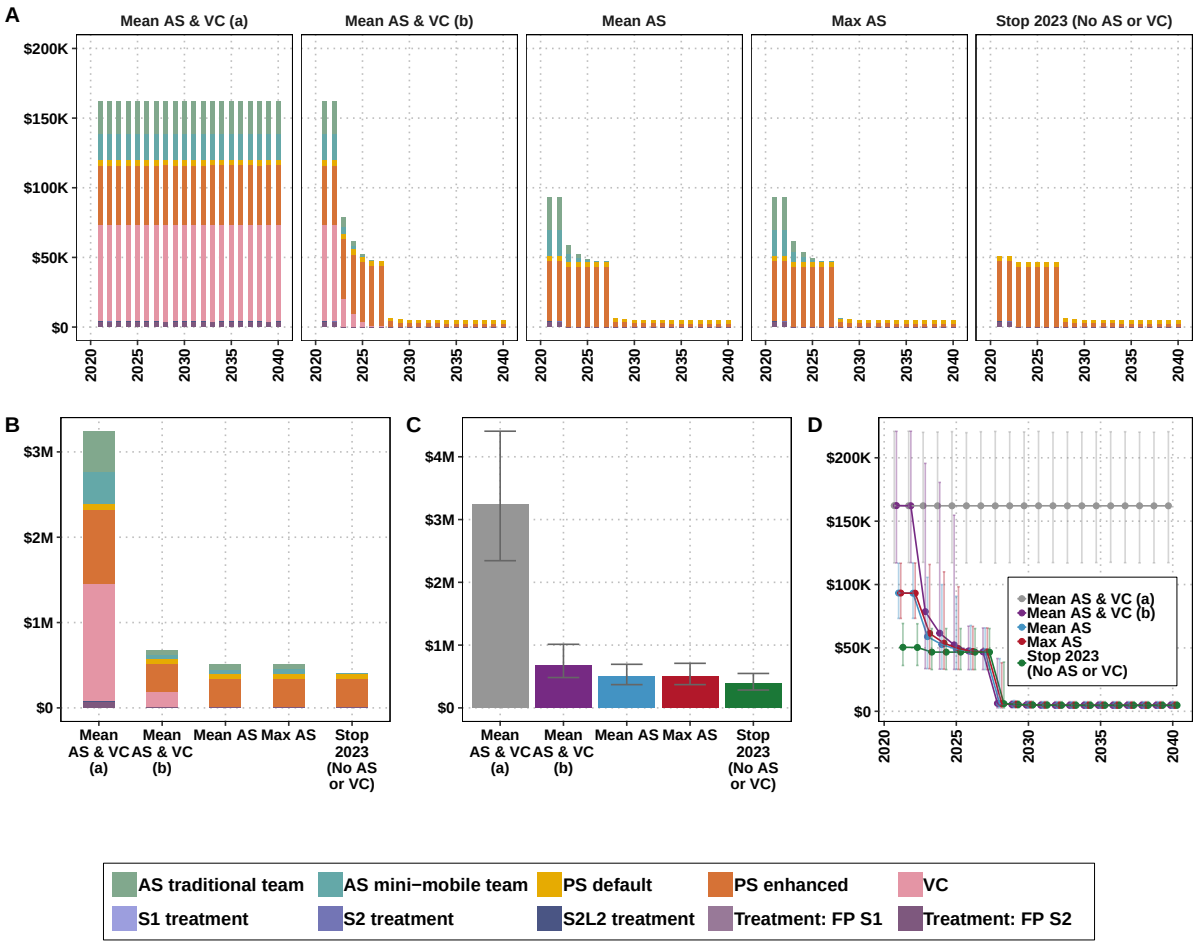

Figure E5: Costs by components of a strategy for the prospective analysis. A) by year, B) for the period of 2021–2040, C) the costs for the period of 2021–2040 with uncertainty, and D) the total spent per strategy per year with 95% prediction intervals. The specificity of the screening algorithm as part of the strategy *Mean AS & VC (a)* is 99.93% and for the strategies *Mean AS & VC (b)*, *Mean AS* and *Max AS* it is 100%. *Stop 2023 (No AS or VC)* signifies that AS and VC stop immediately (it does not occur in 2023 onward). Mean AS is the coverage of people screened for 2000–2019. Max AS is the maximum coverage of people screened for 2000—2019. AS: active screening, PS: passive screening, VC: vector control, FP: false positive, S1: stage 1, S2: stage 2, S2L2: stage 2 rescue treatment.

E5 Glossary of epidemiologic and health economic terms

Box 1: Glossary (adapted from Antillon et. al 2022 [5] under a CC-BY 4.0 license.)

Epidemiology Terms

Intervention Interventions are separate activities to address a health need (e.g. active screening (AS) or vector control (VC)).

Strategy A strategy is a combination of interventions, carried out with a specific coverage, and in parallel. In this paper, we simulate strategies with and without an improvement in PS and with and without VC.

Elimination of transmission (EoT) Globally this is the 2030 goal for gHAT; here we also consider local EoT for health zones. The feasibility of EoT is expressed as a probability equal to the proportion of our simulations in which new infections is zero before a given year (usually 2030).

Disability-adjusted life-year (DALY) In order to present the burden of disease in one common metric across diseases, DALYs are calculated in cost-effectiveness analyses. This is the sum of the years lived with disability due to the disease and the years of life lost by fatal cases. See section S1.4.1.

Health Economics Terms

Parameter uncertainty Uncertainty in the level of transmission or in the costs of interventions and treatment due to unknown underlying parameters (see supplementary section **??** for an explanation of our parameterization of the health outcomes and cost model).

Willingness-to-pay (WTP) or cost-effectiveness threshold The amount of money that payers would pay to avert one DALY arising from the disease in the analysis (gHAT). No specific threshold is recommended, but a recent analysis shows that the WTP in Chad is between $30–518 in 2020 USD per DALY averted [6–8].

Incremental cost-effectiveness ratio A ratio of marginal cost for a marginal benefit, calculated as follows:

$$\text{ICER} = \frac{\Delta\text{Costs}}{\Delta\text{DALYs}} = \frac{\text{Costs}_{\text{strategy}} - \text{Costs}_{\text{next best}}}{\text{Effects}_{\text{strategy}} - \text{Effects}_{\text{next best}}}$$

Not that the ICER is not a strategy against the comparator, but a strategy against the *next best* strategy in terms of costs incurred and DALYs averted.

Cost-effective strategy The strategy where the ICER is less than the WTP (or cost-effectiveness threshold). We say that the cost-effective strategy is "conditional" on the WTP.

Dominated strategy A strategy that costs more than another while yielding worse health outcomes as determined by the DALY calculations. This strategy ought not be implemented.

Weakly dominated strategy (or strategies under extended dominance) A strategy in which the ICER is higher that the next more expensive strategy. Unlike a strongly dominated strategy it costs less than the most expensive strategy, but the cost-per-DALY averted is higher. This strategy ought not be implemented.

Net monetary benefit The net benefits (NMB) framework is derived from ICERs, but also takes uncertainty into account.

$$\text{NMB} \mid \text{WTP} : \text{WTP} \times \Delta\text{DALYs} - \Delta\text{Costs}$$

The optimal strategy at a given WTP is the strategy with the highest mean NMB at that value of WTP.

Optimal strategy Analogous to the cost-effective strategy when no uncertainty is assumed, this is the strategy that is recommended by the NMB framework.